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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,590	TRIGLIA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-25-03 & 3-19-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group II, claims 20-25, in the reply filed on 4-10-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-19 and 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4-10-06.

Applicants' preliminary amendment filed 11-25-03 has been entered. Claims 1-28 are pending and claims 20-25 are under consideration.

Claim Objections

3. Claims 20-25 are objected to because of the following informalities: Claims 20-25 depend from a non-elected claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 20-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "significantly less" in non-elected claims 1 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "significantly less". It is unclear to what extent is "significantly less". The specification fails to define the term "significantly less". Claims 20-25 depend from the non-elected claim 1 but fail to clarify the indefiniteness.

The phrase "blood-borne molecules" in line 8 of claim 22 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "blood-borne molecules". The specification fails to specifically define the phrase "blood-borne molecules". Claims 23-25 depend from claim 22 but fail to clarify the indefiniteness.

The phrase "release of molecules" in lines 8-9 of claim 22 is vague and renders the claim indefinite. It is unclear what molecules are released from the cells, the blood-borne molecules or molecules other than the blood-borne molecules. Claims 23-25 depend from claim 22 but fail to clarify the indefiniteness.

6. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: What is the use of the cells of the cell line of claim 1. The preamble of the claim indicates using cells of the cell line of claim 1, however, the method steps only refer to culturing the cells in a bio-artificial device, but it is unclear what would be the purpose of using the cells and how to use the cells.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 20-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 20-25 are directed to a bio-artificial liver device comprising an apparatus containing cells of the cells line of claim 1, wherein said cells are cultured in serum-free medium (SFM) on a surface of said device to sustain a subject having a liver disorder or compromised liver function, a method of using said cells, and a method of treating a subject having a compromised liver function by using said bio-artificial liver device either inside or outside said subject for removal of blood-borne molecules entering said device and release of molecules from said cells into blood exiting said device. Claim 25 specifies the subject is a human.

The specification discloses the establishment of a clonal C3A cell line 2.5B1 cultured in serum-free medium and has less than 70% of doubling time of the parent C3A cell line, detection of gluconeogenesis, glycogen synthesis and the synthesis of antichymotrypsin, antitrypsin, antithrombin III, complement C3, factor V and transferrin in said cell line. Claims 20-25 encompass using any cell line, derived from parent C3A cell line, cultured in serum-free medium with doubling time significantly less than the doubling time of parent C3A cell line for treating a subject having compromised liver function.

The specification fails to disclose the establishment of any C3A clonal cell line other than the disclosed 2.5B1 cell line cultured in serum-free medium which has significantly less than the doubling time of parent C3A cell line, and shows the liver specific biological functions including gluconeogenesis, glycogen synthesis, and the synthesis of antichymotrypsin, antitrypsin, antithrombin III, complement C3, factor V and transferrin. It is unclear whether the establishment of 2.5B1 cell line, ATCC Accession No. CRL-12461, recited in the specification is reproducible. The specification fails to demonstrate that the establishment of the serum-free cell line from parent C3A cell line is reproducible. Various serum-free media have been used to produce clonal C3A cell line and not every serum-free medium (SFM) is able to produce a C3A clonal cell line which grows in a serum-free medium. The cells grown in Gibco's Hepatozyme SFM and HyClone's HyQ-CCM4 serum-free medium exhibited round up appearance which was attributed to a loss of surface adherence (see specification page 22-23). Further, the cells grown under different serum-free media have various growth rates and the JRH Bioscience's ExCell 620 serum-free medium gives the most consistent growth of the C3A clonal cells. The specification only mentions growing C3A cells in Gibco's Aim V medium or Irvine Scientific's IS293 medium, but there is no evidence of record indicates that growing C3A cells in Gibco's Aim V medium or Irvine Scientific's IS293 medium can produce cell lines that has a doubling time in SFM less than about 70% of or significantly less than the doubling time of the parental C3A cell line in SFM. Different serum-free medium could result in different phenotypes of the cells and even same serum-free medium could result in different growth rate of the clonal cells. It would be unpredictable whether serum free medium other than JRH Bioscience's ExCell 620 would produce desired clonal C3A cells or cell lines that have doubling times less than 70% of

or significantly less than the doubling time of the parent C3A cells in SFM, and shows the liver specific biological functions including gluconeogenesis, glycogen synthesis, and the synthesis of antichymotrypsin, antitrypsin, antithrombin III, complement C3, factor V and transferrin. Thus, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over full scope of the invention claimed.

The specification also encompasses culturing any clonal C3A cells on various type of bio-artificial device made of different materials and designs to treat numerous different liver disorders or diseases in a subject with said device outside or inside said subject. The specification fails to provide adequate guidance and evidence for whether any clonal C3A cell line, having doubling time significantly less than that of parental C3A cells in SFM, can be cultured in or on any bio-artificial device to produce sufficient clonal C3A cells in SFM so as to provide sufficient liver specific biological activity for removal of blood-borne molecules in the blood of a subject having compromised liver function and to treat said subject with said device outside or inside said subject. Strain et al., 2002 (Science, Vol. 295, p. 1005-1009) reports a bioartificial liver (BAL) must provide a number of crucial liver functions including synthesizing many proteins, such as clotting factors, producing bile, regulating carbohydrate, fat and protein metabolism, detoxifying ammonia product and breaking down alcohol and drugs. "The problem is deciding which liver functions are the most important and should be carried out by the BAL bioreactor" (middle column, p. 1005). Strain points out that primary hepatocyte loses liver-specific gene expression and become phenotypically unstable in culture and non-parenchymal liver cells and bile duct epithelial cells are important for optimal hepatic activity, and "[t]he enormous scale-up required to use BAL devices clinically is problematic: At least 10^{10}

hepatocytes in a BAL bioreactor would be needed to support a patient's failing liver (right column, p. 1005). The claims read on using the clonal C3A cells for treating a subject having compromised liver function alone. The specification fails to provide adequate guidance and evidence whether the clonal C3A cells are phenotypically stable and can provide sufficient liver specific biological activities without the presence of non-parenchymal liver cells and bile duct epithelial cells for optimal hepatic activity as taught by Strain, and whether sufficient number of clonal C3A cells could be cultured on the BAL to support a patient's failing liver. Further, "[t]he ideal BAL design must ensure optimal ex vivo maintenance of hepatocytes. It has been assumed, but not yet proven, that simple "flow through" BAL systems achieve this. However, given that conventional monolayer cultures cannot optimally maintain hepatocytes, it is likely that hepatocytes will need to be induced to form cellular aggregates in which they reacquire their polarization (middle column, p. 1006). "The greatest challenge for the BAL bioreactor is how best to maintain viable functional hepatocytes outside of the body" and "[I]nteractions among the different types of hepatic cell populations are essential for the liver to operate appropriately. Coculture of hepatocytes with nonparenchemal liver cells has been shown to be beneficial (5). The downside is that inclusion of other cell types would inevitably make BAL design, construction, and handling even more complex" (right column, p. 1007). The claims do not recite what kind of bio-artificial liver device would be used. The specification fails to provide adequate guidance and evidence for whether the clonal C3A cells alone would form a monolayer of cells or form cellular aggregates in which type of BAL device, and whether the clonal C3A cells would be able to provide sufficient liver specific biological activities for treating a subject having compromised liver function.

Strain further points out that C3A hepatocyte line, a subclone of the HepG2 hepatoblastoma cell line, has been used in clinically testing BAL device, however, "the safety aspects of using genetically altered and potentially tumorigenic liver cells in the clinic still needs to be addressed (left column, p. 1006). Claim 25 specifies the subject is a human. The specification fails to provide adequate guidance and evidence whether the use of clonal C3A cells in BAL device for treating a human would induce tumor formation in said human subject. Although BAL bioreactors have been tested in a number of different small and large animal models of liver failure, however, "interpreting the data from experimental studies and extrapolating them into the clinic has proved difficult" (left column, p. 1007).

In addition, a subject having compromised liver function includes a subject having numerous different liver disease or disorders. Different liver diseases or disorders differ pathologically, morphologically and physiologically, and the mechanisms that result in compromised liver function could vary dramatically in different liver diseases or disorders. The specification fails to provide adequate guidance for the correlation between removal of blood-borne molecule entering the device as well as release of molecules from the cells and treatment of a subject having compromised liver function. It is unclear what kind of blood-borne molecules should be removed from the blood entering the artificial device and what kind of molecules should be released from the cells into blood exiting said device so as to provide therapeutic effect for treating a subject having compromised liver function. It is also unclear whether sufficient clonal C3A cells can be cultured on or in the bio-artificial device and whether sufficient liver specific biological activity could be provided to recover the compromised liver function for treating a subject having compromised liver function. Absent the specific guidance,

one skilled in the art at the time of the invention would not know how to use any clonal C3A cells on various types of bio-artificial device to treat numerous different liver disorders or diseases in a subject with said device outside or inside said subject.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the level of the ordinary skill which is high, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiering, et al., 1994 (In Vitro Cellular and Developmental Biology Animal, Vol. 30A, No. 3, Part 2, pp. 106) in view of Price et al., US Patent No. 6,103,529.

Claims 20 and 21 are directed to a bio-artificial liver device comprising an apparatus containing cells of the cells line of claim 1, wherein said cells are cultured in serum-free medium (SFM) on a surface of said device to sustain a subject having a liver disorder or compromised liver function, and a method of using said cells comprising culturing said cells in said device in serum-free medium.

Spiering teaches "Hepatix C3A cells are being used as the foundation for an extracorporeal liver assist device (ELAD) with the intention of supplying sufficient liver function to support patient in fulminant hepatic failure". Spiering teaches culturing hepatix C3A human hepatoblastoma cells in a hollow fiber bioreactor.

Spiering does not teach growing C3A cells in serum-free medium.

Price teaches using serum-free medium (SFM) to overcome the drawbacks of the use of serum or animal extracts, such as variation of chemical composition and possible contamination of infectious agent, and the availability of commercial SFM for culturing hepatocytes (e.g. column 2, 3). Price also teaches that cultured cells can be engineered to produce large quantities of biological substances, such as monoclonal antibodies, growth factors, and hormones, via recombinant DNA technology (e.g. column 1).

It would have been obvious for one of ordinary skill at the time of the invention to culture the Hepatix C3A cells in a bioreactor as taught by Spiering with SFM as taught by Price because Price teaches culturing hepatocytes using SFM and Hepatix C3A cells are derived from

hapatocytes. Since the claimed clonal C3A cells are obtained by growing the C3A cells in SFM, therefore, when one of ordinary skill in the art culture C3A cells in SFM it is inherent that the resulting clonal C3A cells would have doubling time in SFM significantly less than the doubling time of the parent C3A cells in SFM as claimed in the instant invetnion.

One having ordinary skill at the time the invention was made would have been motivated to culture C3A hepatocyte cells in a bioreactor in SFM to adapt for normal growth and maintenance in order to avoid the drawbacks of the use of serum or animal extracts in a medium, such as variation of chemical composition and possible contamination of infectious agent, and to produce large quantities of biological substances, such as monoclonal antibodies, growth factors, and hormones, via recombinant DNA technology as taught by Price, or used as the foundation for an extracorporeal liver assist device as taught by Spiering with reasonable expectation of success.

It should be noted that the intended use of the bio-artificial liver device in claim 20 does not carry weight in 35 U.S.C. 103(a) rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER